REMARKS

Applicants respectfully request entry of the foregoing and reconsideration of the subject matter identified in caption, as revised, pursuant to and consistent with 37 C.F.R. §1.112, and in light of the remarks which follow.

Claims 16-21 and 35-46 are pending in the application. Applicants submit herewith various revisions to the claims to more particularly point out and distinctly claim what applicants believe to be their invention. Support for the revisions to claim 16 is found at least on page 6, paragraphs [0023] and [0024], of the application as filed.

New claims 47 and 48 have been introduced. Support for these claims is found at least on page 7, paragraphs [0027] and [0028], of the application as filed, which includes the inherent feature of the well-known $C_{20}H_{28}O$ molecular formulas of 11-cis-retinal and 9-cis-retinal, as well as on page 9, lines 3-9.

35 USC § 112:

The Official Action asserts a deficiency in the written description. It is argued that the phrase "an opsin-binding synthetic retinoid" is functional language not supported by sufficient structural features. Applicants respectfully disagree, and traverse the rejection.

"There is nothing inherently wrong with defining some part of an invention in functional terms. Functional language does not, in and of itself, render a claim improper." MPEP 2173.05(g) (citation omitted). Thus, to the extent the rejection is based only on the use of functional language, the rejection is improper and should be withdrawn.

Additionally, the inclusion of claims 19, 20, 21, and 38-43 in that rejection is also improper as those claims recite specific classes of retinoid compounds having common features, i.e., 9-*cis*-retinal and/or 11-*cis*-retinal, which features applicants have shown to be associated with mutant opsin binding and stabilizing properties, and an amelioration of loss of photoreceptor function. *See, e.g.,* ¶¶ 0077 - 0080. These claims thus feature retinoid compounds that are clearly described within the instant application.

Applicants have revised claim 16 to include features that more specifically recite the form of mutant opsin expressed in a human subject. Various classes of compounds that stabilize the mutant opsin are disclosed throughout the specification. Applicants have identified a class of compounds, and have identified features shared by that class that are associated with desirable properties. The specification provides a thorough written description as to what those features are, and have described the class of compounds within the specification. As an example, new claims 47 and 48 feature synthetic retinoids containing the carbon backbones of 11-cis-retinal and 9-cis-retinal. These backbones are specific structural features common to all synthetic retinoids featured in these claims.

Applicants are not obligated to specifically disclose each member of that class of compounds, nor are they obligated to test all members of such class. *See, e.g., In re Marzocchi,* 439 F.2d 220 (CCPA 1971); *see also* MPEP 2163.04 ("A description as filed is presumed to be adequate unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption."). The rejection presents no evidence or reasoning rebutting applicants' disclosure and characterization of the compounds capable of binding and stabilizing the specified

class of mutant-opsin-binding retinoids. As such, applicants' disclosure must be taken at face value for what it reasonably teaches one skilled in the art.

Additionally, the instant rejection does not appear to adequately consider knowledge in the art regarding synthetic retinoids and derivatives of 11-cis-retinal and 9-cis-retinal. For example, the cited document by Chatzinoff et al. (addressed further below) reports the use of retinol (vitamin A), which is the alcohol form of retinal, as well as the use of retinol esters.

Finally, aside from the fact that applicants have provided a clear written description of a class of compounds consistent with the terminology of the claims, they have also disclosed methods of screening compounds within that class for opsin-binding and stabilization, and they have demonstrated that compounds within that class possess the desired properties. From the specification, it would have been clear to one skilled in the art what those screens are, and how to use them successfully to identify additional opsin-binding synthetic retinoids. The screens provide quantitative assessment of mutant-opsin rescue, with respect to folding, processing, photobleaching, isomerization, pigment formation and stability. Assessment of photoreceptor activity is measurable, and those techniques would have been readily accessible and useful to one skilled in the art.

In view of the foregoing, applicants' written description of the invention is presented in the specification in such full, clear, concise and exact terms as to demonstrate possession to one skilled in the art. Accordingly, applicants respectfully request reconsideration and withdrawal of the rejection.

Claims also stand rejected as indefinite for use of the term "ameliorate." Applicants traverse the rejection.

The term "ameliorate" has a definite and clear meaning, and would have been readily understood by those skilled in the art, particularly those involved in the treatment of disease. While applicants acknowledge that the term is somewhat broad, it is not indefinite. Breadth alone is not an adequate basis to support a § 112, first paragraph rejection. MPEP §2173.04 ("Breadth of a claim is not to be equated with indefiniteness. (citation omitted)). Applicants also note that there are issued US patents using that term without further definition, and, of those at least two involve retinitis pigmentosa, i.e., USPN 7,259,180 and 6,225,291.

Without acquiescence to the instant rejection, Applicants have removed the term "ameliorate" from the claims in favor of the term "treating," which is not intended, or believed, to narrow the scope of the claim. In view of the claim revisions, Applicants request reconsideration and withdrawal of the rejection.

The claims also stand rejected as indefinite, it being asserted that "it is unclear what conditions by which loss of photoreceptor function are envisioned." Applicants urge that the foregoing revised claims moot the rejection as it is now recited that the loss of photoreceptor function is due to endogenous expression of P23H mutant opsin protein. The P23H mutant protein suffers improper folding, which produces deleterious effects such as the formation of aggresomes, and resultant loss of photoreceptor function. Applicants have discovered that the deleterious effects - and loss of photoreceptor function – in a subject can be substantially diminished or eliminated by administering a synthetic retinoid to that the subject. Without being bound by theory, the mutant opsin protein in the subject is

stabilized by this treatment. Therefore, Applicants request reconsideration and withdrawal of the rejection.

It is also asserted that the claims are indefinite as to whether the opsin protein is part of the pharmaceutically acceptable vehicle. Applicants urge that one skilled in the art reading the claim would have understood that the synthetic retinoid is the therapeutic agent to be carried within the pharmaceutically acceptable vehicle. Nonetheless, applicants have revised the claim for other reasons, and urge that the claim as revised moots the rejection.

35 USC § 102:

Van Hooser et al, "Rapid restoration of visual pigment...", PNAS (2000) "VH I" is directed to RPE65 deficient mice that are administered 9-cis-retinal. The rejection asserts that "Van Hooser et al. teaches the use of 9-cis-retinal ... for the treatment of lack of 11-cis-retinal...." VH I acknowledges a number of molecular defects in RPE65 deficient mice, and "absence of 11-cis-retinal" is but one. Thus, it is unclear how or why the pharmacological intervention of VH I improves the condition of RPE65 deficient mice.

The instant claims have been modified to more specifically recite the treatment of subjects suffering from endogenous expression of P23H mutant opsin protein. Applicants teach, among other things, that the administration of 9-cis- and/or 11-cis-retinals can stabilize the opsin to more closely resemble native folding so it can perform its native role. There is not shown to be any teaching in VH I of administering 9-cis-retinal and/or 11-cis -retinal to subjects suffering from expression of the P23H mutant opsin protein. Accordingly, there is no showing that VH I

teaches the claimed invention, expressly or inherently. Applicants respectfully request reconsideration and withdrawal of the rejection over VH I.

Van Hooser et al., "Recovery of Visual Functions...", J. Biol. Chem. (2002) "VH II" also involves RPE65-/- mice, and describes administration of 9-cis-retinal in an effort to improve and/or restore light sensitivity. As above, the rejection asserts that the reference "teaches the use of 9-cis-retinal ... for the treatment of lack of 11-cis-retinal." Again, without conceding the point, the assertion is no longer relevant in view of the present revisions to the claims. As revised, claim 16 features the administration of synthetic retinoids to subjects suffering endogenous expression of the P23H mutant opsin protein. This is distinct from a subject suffering from lack of endogenous production of 11-cis-retinal.

VH II is silent as to the use of 9-cis-retinal for subjects suffering from P23H mutant opsin production, and there has not been shown to be any such administration to such subjects in VH II. Accordingly, there is no *prima facie* case of anticipation. Applicants respectfully request reconsideration and withdrawal of the rejection.

Chatzinoff et al. (USPN 3,196,078) purportedly describes a composition "useful in the disease retinitis pigmentosa." Col. 1, lines 12-13. The document fails to teach or suggest treatment of a P23H mutant opsin protein. The document fails to provide any linkage between this specific mutant opsin protein and the disease retinitis pigmentosa. So there is also no evidence that Chatzinoff et al. *necessarily* disclose treatment of a subject with such a mutant opsin protein.

To the contrary, subsequent work negates the portions of document being relied upon. In 1968, Chatzinoff published a "Negative Study" retracting statements

regarding the utility of 11-cis isomer of vitamin A in RP. Chatzinoff, et al., Arch. Opthal., vol 80, Oct. 1968, 417-419 (Chatzinoff II; Second Information Disclosure Statement, submitted herewith). Specifically, Chatzinoff II reported that "11-cis vitamin A is not of value in the treatment of retinitis pigmentosa." Chatzinoff II at p. 419. Therefore, the retinitis pigmentosa studied by Chatzinoff was distinct from the P23H mutant opsin protein featured in the claims.

For at least the foregoing reasons, Chatzinoff et al. do not anticipate the present claims.

35 USC § 103:

Chatzinoff et al. with Kuksa et al. and/or Klimko

Likewise, Chatzinoff et al. do not render the claimed invention obvious, either alone or in combination with the other cited references. As pointed out above, Chatzinoff et al. provide no linkage between the report on retinitis pigmentosa treatment and treating the mutant opsin featured in the pending claims. Additionally, Chatzinoff et al. provide no expectation of success in practicing the claimed invention.

To the contrary, Chatzinoff's own subsequent work teaches away from the claimed invention. As explained above, Chatzinoff subsequently published a "Negative Study" retracting statements regarding the utility of 11-cis isomer of vitamin A in RP (Chatzinoff II; Second Information Disclosure Statement, submitted herewith). There, Chatzinoff II reported that "11-cis vitamin A is not of value in the treatment of retinitis pigmentosa." Chatzinoff II at p. 419.

Additionally, Chatzinoff et al. also do not suggest the claimed invention, either alone or in combination with Kuksa and/or Klimko.

The examiner asserts that "Kuksa et al. teaches that the constrained retinoids particularly the 11-cis-7 retinal has potential use to inactivate opsin in some retinal degeneration diseases." (emphasis added). By that reasoning alone, Kuksa et al. teaches away from the claimed invention. Applicants have taught, and now claim, the treatment of mutant opsin proteins by a method that, among other things, stabilizes the mutant opsin such that it more closely resembles natural or wild-type opsin. In this way, mutant opsin functionality is restored and loss of photoreceptor function is likewise diminished. Thus, one skilled in the art reading Kuksa et al. would have found no motivation to combine Kuksa et al. with Chatzinoff et al. Even assuming, for the sake of argument only, that one were so motivated, there has been no showing that one would have arrived at the instant invention, or would have thought to employ it in the case of the featured P23H mutant opsin protein.

Kuksa et al. more specifically state that "[wildtype] Rho regenerated with 11-cis-7-ring isomer has only 0.1% of wild type activity; it is also inactive in both sensitive ERG and FTIR experiments." One skilled in the art would have appreciated that Kuksa et al. are stating that 11-cis-7-ring retinal "does not activate G-protein in vivo and in vitro, and that it does not isomerize along other double bonds, suggesting that it fits tightly into the binding site of opsin", forming a stable 11-cis-7-ring-Rho.

The therapeutic benefit reported by Kuksa et al. is the use of the 11-cis-7-ring isomer to block the signal transduction process of rods, and that by sparing their demise at the cellular level, it may be possible to prolong the survival of the cones.

In contrast, the claimed treatment has the goal of generating functional Rho, not to inactivate it as described by Kuksa et al. This difference in outcome is

achieved in part based on the difference in stability of the mutant Rho relative to wild-type Rho. Specifically, 11-cis-7-ring-retinal spontaneously releases from mutant opsin, while remaining irreversibly bound to the wild-type opsin. This functional difference in interaction results in the 11-cis-7-ring-retinal being an inverse agonist of wild-type opsin (as shown by Kuksa et al.), while acting to pharmacologically rescue mutant opsin through its stabilization during processing, followed by its spontaneous release to allow binding of the natural retinoid.

Klimko is relied upon as purportedly disclosing pharmaceutical formulations for treating ophthalmic conditions. The reference does not otherwise cure the above-identified deficiencies of the other references, and so its combination with those references does not render the claimed invention obvious.

The combination of Chatzinoff et al., Kuksa et al., and Klimko does not teach or suggest the claimed invention. In particular, it does not teach or suggest treatment or stabilization of a P23H mutant opsin protein, nor does it provide any teaching or suggestion how or why one might achieve it. As such, there is no teaching or suggestion, or apparent motivation, to use the claimed synthetic retinoids to treating subjects suffering expression of P23H mutant opsin protein. Further, the documents, when taken as a whole and in proper context, teach away from the claimed invention. For example, Chatzinoff et al.'s own subsequent work reports the futility of using the specified vitamin A derivatives in treating retinitis pigmentosa; and Kuksa et al. teach away from the use of the retinal to stabilize and diminish a loss of photoreceptor function in the specified subjects. Accordingly, the cited combination of documents would not have led one skilled in the art to expect that treatment of

subjects suffering expression of P23H mutant opsin protein would have benefited from the claimed method of treatment.

Double Patenting

The Official Action asserts a *provisional* double patenting rejection over co-owned, co-pending application 10/548,612. The revision of claim 16, as presented herein, clarifies that the indication of the claimed treatment method is expression of mutant opsin (P23H mutant opsin), and is therefore an express element of the claimed invention. The instant revisions moot the rejection. Applicants respectfully request reconsideration and withdrawal of the double patenting rejection.

Conclusion

In view of the foregoing revisions and remarks, applicants respectfully request reconsideration and withdrawal of all outstanding rejections. Applicants submit that the claims are now in condition for allowance, and respectfully request formal notification to that effect. If, however, the Examiner perceives any impediments to such a notice of allowability, whether substantive or formal, the Examiner is encouraged to call Applicants' attorney at the number provided below. Such informal communication will expedite examination and disposition of this case.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

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